KOKAI (Japanese Unexamined Patent Publication) No. 3-240729
Title of the Invention: Oral Solid Preparation with Accelerated Absorption
Publication Date: October 28, 1991
Patent Application No. 2-33491
Filing Date: February 14, 1990
Applicant: Taisho Pharmaceutical Co., Ltd.
Inventors: Masami Nemoto, Hidefumi Hayashi, Shigeru Itai, Yasuo Nakagawa, Yoko Katayama

CLAIMS

1) An oral solid preparation containing one or more types of antacids that accelerates the absorption of oxicam antiinflammatory drugs.

2) An oral solid preparation as set forth in claim 1 wherein said oxicam antiinflammatory drug is chlortenoxicam, tenoxicam or piroxicam.

3) An oral solid preparation as set forth in either of claims 1 or 2 wherein said antacid is sodium hydrogen carbonate, calcium hydrogen phosphate, aluminum magnesium metasilicate, magnesium oxide or synthetic hydrotalcite.

DETAILED DESCRIPTION OF THE INVENTION

[Field of Utilization in Industry]

The present invention relates to an oxicam antiinflammatory agent expected to demonstrate rapid action.

[Prior Art]

Technology that has examined the rapid action of oxicam antiinflammatory agents is not known in the prior art.

[Problems to be Solved by the Invention]

Thus, there have been no preparations of oxicam antiinflammatory agents that are satisfactory for

conditions requiring rapid absorption such as toothache and other pain.

[Means for Solving the Problems]

The inventors of the present invention found a preparation having good solubility, extremely fast onset of absorption in humans and minimal variation by blending certain types of antacids, thus leading to completion of the present invention on the basis of that finding.

The present invention is an oral solid preparation that contains one or more types of antacids that accelerates the absorption of oxicam antiinflammatory drugs.

Examples of antiinflammatory agents used in the present invention include chlortenoxicam, tenoxicam and piroxicam.

Examples of antacids used in the present invention include sodium hydrogen carbonate, calcium hydrogen phosphate, aluminum magnesium metasilicate, magnesium oxide and synthetic hydrotalcite.

Although varying according to the type of oxicam antiinflammatory drug and the type and form of antacid, the blended amount of antacid used in the present invention is preferably 10-50 parts by weight to 1 part by weight of oxicam antiinflammatory drug, and more preferably 10-40 parts by weight.

For example, in the case of tablets, solubility is improved by blending at least 1 part by weight of sodium hydrogen carbonate to 1 part by weight of chlortenoxicam, and if 10 parts by weight or more are blended, solubility is improved significantly. However, if more than 20 parts by weight are blended, hardness decreases thereby preventing suitable tablets from being obtained, and if more than 15 parts by weight are blended, the tablets are subject to problems in terms of forming such as cracking or chipping during coating.

The forming problems caused by this sodium hydrogen carbonate can be solved to a certain extent by blending at least two types of antacids such as calcium hydrogen phosphate.

In addition, if synthetic hydrotalcite is used, although solubility is improved by blending 15 parts by weight or more of hydrotalcite to 1 part by weight of chlortenoxicam, if more than 40 parts by weight are blended, the adsorption of chlortenoxicam intensifies resulting in decreased solubility and absorption.

On the other hand, in the case of granules, it is preferable to blend 20-40 parts by weight of aluminum magnesium metasilicate to 1 part by weight of chlortenoxicam, and more preferably 15-30 parts by weight of aluminum magnesium metasilicate. If more than 40 parts by weight are blended, however, granulation becomes difficult, thereby preventing the production of granules having good fluidity. In addition, in the case of sodium hydrogen carbonate, although solubility is improved by blending at least 1 part by weight of sodium hydrogen carbonate to 1 part by weight of chlortenoxicam, if more than 20 parts by weight are blended, the ease of forming of the granules becomes poor causing the surface of the granules to chip during coating.

Next, typical production processes can be used to produce the preparation of the present invention for both tablets and granules. For example, granules can be made by adding antacid to oxicam antiinflammatory drug, crushing, adding a vehicle (e.g., sugars such as lactose and glucose, sugar-alcohols such as D-sorbitol and mannitol, celluloses such as microcrystalline cellulose, powders such as cornstarch, or aerozil), disintegrating agent (e.g., celluloses such as calcium carboxymethylcellulose and low substituted hydroxypropylcellulose, polyvinylpyrrolidone or sodium

4

cross-calomelose), and a binder (e.g., celluloses such as hydroxypropylcellulose, hydroxypropylmethylcellulose, ethylcellulose and methylcellulose, or vinylpyrollidone), mixing or pulverizing, and forming into granules in a mixture of alcohol and purified water. A stirring granulator, fluid bed granulator, kneader, rolling granulator, centrifugal fluid granulator, extrusion granulator or vacuum granulator can be used for granulation. Next, the formed granules are dried to prepare powders, grains and granules.

Capsules and tablets are manufactured by adding a lubricant (e.g., magnesium stearate, calcium stearate, talc and hardened oil) to granules.

Furthermore, grains, granules and tablets can be made even easier to take by coating.

[Effect of the Invention]

According to the present invention, the rapid action of antiinflammatory drugs is remarkably improved, making it useful for conditions requiring rapid absorption such as toothache and other pain.

[Embodiments]

The following provides a detailed explanation of the present invention through its embodiments and test examples.

Embodiments 1-8

Table 1 Prescription Examples of Embodiments 1-8

Ingredient	Prescription No.							
	1	2	3	4	5	6	7	8
Chlortenoxicam	2	2	2	2	2	2	2	2
Sodium hydrogen carbonate	2.5	5.0	7.5	10	15	20	30	40
Lactose	37.5	35.0	32.5	30	25	25	10	0
Microcrystalline cellulose	41.5	41.5	41.5	41.5	41.5	41.5	41.5	41.5
Aerozil	1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0
Low-substituted hydroxypropyl-cellulose	10	10	10	10	10	10	10	10
Hydroxypropyl-cellulose	5	5	5	5	5	5	5	5
Magnesium stearate	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5
Total	100	100	100	100	100	100	100	100

(Units: mg)

Tablets were manufactured based on prescriptions 1-8 shown in Table 1 while changing the blending ratios of chlortenoxicam and sodium hydrogen carbonate.

The preparation method was as described below. Namely, after first mixing and crushing chlortenoxicam and sodium hydrogen carbonate, lactose, microcrystalline cellulose, aerozil, low-substituted hydroxypropylcellulose and hydroxypropylcellulose were mixed in. Next, the mixture was added to a stirring granulator (particle granulator; Fuji Sangyo) followed by the addition of a mixed solution of alcohol and purified water. The mixture was then granulated at a blade speed of 300 rpm and cross screw speed of 1000 rpm. After drying with a fluid bed dryer, the granules were graded to 20 mesh or less using a speed mill.

Magnesium stearate was then added to the graded granules and after mixing well, tablets having a diameter of 7 mm were formed by a tablet forming machine.

Embodiment 9 (Prescription 9)	
Chlortenoxicam	2 mg
Sodium hydrogen carbonate	20 mg
Anhydrous calcium hydrogen phosphate GS	50 mg
Microcrystalline cellulose	40 mg
Aerozil	2.5 mg
Low-substituted hydroxypropylcellulose	25 mg
Hydroxypropylcellulose	10 mg
Calcium stearate	0.5 mg
Total	150 mg

Tablets were produced in the same manner as the production process described in Embodiments 1-8 based on the above-mentioned prescription.

Embodiments 10 and 11

Table 2

Examples of Prescriptions of Embodiments 10 and 11

Ingredients	Prescription No.	
	10	11
Tenoxicam	10	0
Piroxicam	0	10
Sodium hydrogen carbonate	100	100
Anhydrous calcium hydrogen phosphate GS	100	100
Low-substituted hydroxypropyl-cellulose	20	20
Aerozil	5.5	5.5
Hydroxypropylcellulose	14	14
Magnesium stearate	0.5	0.5

4

(Units: mg)

Tablets were manufactured based on prescriptions 10 and 11 shown in Table 2 while changing the blending ratios of tenoxicam and piroxicam.

The preparation method was as described below. Namely, after first mixing and crushing tenoxicam or piroxicam and sodium hydrogen carbonate, anhydrous calcium hydrogen phosphate GS, low-substituted hydroxypropylcellulose, aerozil and hydroxypropylcellulose were mixed in. Next, the mixture was added to a stirring granulator (particle granulator; Fuji Sangyo) followed by the addition of a mixed solution of alcohol and purified water. The mixture was then granulated at a blade speed of 300 rpm and cross screw speed of 1000 rpm. After drying with a fluid bed dryer, the granules were graded to 20 mesh or less using a speed mill. Magnesium stearate was then added to the graded granules and after mixing well, tablets having a diameter of 7 mm were formed by a tablet forming machine.

Embodiment 12

Granules produced according to a typical production process based on Prescription 9 were filled into No. 3 hard capsules to obtain a capsule preparation.

Embodiment 13

Granules produced according to a typical production process based on Prescription 10 were filled into No. 3 hard capsules to obtain a capsule preparation.

Embodiment 14

Granules produced based on Prescription 11 were filled into No. 3 hard capsules to obtain a capsule preparation.

Test Example 1 (Tablet Elution Test)

(Samples)

One tablet each of Samples 1-9 and Embodiments 1-9 was used.

Control sample: One each of the tablets described below.

(Prescription)

Chlortenoxicam	2 mg
Lactose	40 mg
Microcrystalline cellulose	41.5 mg
Aerozil	1 mg
Low-substituted hydroxypropylcellulose	10 mg
Hydroxypropylcellulose	5 mg
Magnesium stearate	0.5 mg
Total	100 mg

Tablets were produced in the same manner as Embodiment 2 based on the above-mentioned prescription.

(Test Method)

An elution test in artificial gastric juice was conducted using the paddle method (100 rpm). 900 ml of Solution I (pH 1.2) of the Disintegration Test of the General Test Methods of the Japanese Pharmacopoeia (37∞C) was used for the artificial gastric juice. In addition, determination of the amount of primary drug that eluted from the tablets was performed by optical absorbance.

(Results)

The results are shown in Table 3.

Table 3 Solubility in Artificial Gastric Juice

Prescription No.	Time (min)					
	5	10	15	20	30	60
1	32.3	41.5	48.5	54.5	60.2	75.5
2	34.5	42.3	49.5	55.6	61.5	75.5
3	47.5	58.5	62.3	66.6	74.0	83.5
4	60.0	66.5	69.5	73.5	80.0	90.5
5	70.5	75.5	79.5	82.1	84.5	92.5
6	80.0	100.1	102.1	102.5	102.6	102.5
7	82.1	100.3	100.5	100.4	101.1	101.5
8	40.2	72.3	90.1	100.0	100.9	101.9
9	100.8	101.6	101.6	102.5	101.6	101.6
Control	10.0	18.5	23.8	30.0	40.0	52.3

(Units: %)

As shown in Table 3, in comparison with prescriptions completely free of sodium hydrogen carbonate, Samples 6 and 7 exhibited remarkably improved solubility. In addition, as the ratio of sodium hydrogen carbonate to chlortenoxicam increased, the solubility of the primary drug improved. However, in the case of Prescription 8, initial solubility was lower than Prescriptions 6 and 7. This is due to the tablet having floated on the surface during the elution test resulting in a delay in tablet disintegration. In addition, the reason for the tablet floating on the surface is believed to be due the use of microcrystalline cellulose which has a lower specific gravity than lactose.

The solubility in artificial gastric juice of Prescription 9 was observed to demonstrate 100% elution in 5 minutes.

Test Example 2 (Capsule Elution Test)

(Samples)

Sample 1: One capsule of Embodiment 12

Sample 2: One capsule of Embodiment 13

Sample 3: One capsule of Embodiment 14

(Test Method)

An elution test in artificial gastric juice was conducted. Furthermore, the elution test was conducted using the paddle method (100 rpm), and 900 ml of Solution I (pH 1.2) of the Disintegration Test of the General Test Methods of the Japanese Pharmacopoeia (37∞C) was used for the artificial gastric juice. In addition, determination of the amount of primary drug that eluted from the capsules was performed by optical absorbance.

(Results)

The results are shown in Table 4.

Table 4 Solubility of Capsule Preparations

Sample No.	Time (min)				
	5	10	20	30	60
1	100.5	101.5	101.4	102.4	101.6
2	100.8	101.6	101.6	102.1	102.1
3	102.1	102.1	102.8	102.5	102.5

(Units: %)

The capsules exhibited solubility similar to that of the tablets.

Test Example 3

(Samples)

Sample 1: One tablet of Embodiment 9

Control sample: One tablet of the control sample used in Test Example 1

(Test Method)

An absorption experiment was performed according to the crossover method on 6 healthy volunteers.

(Results)

The results are shown in Table 5.

11

Table 5 Pharmacodynamic Parameters

Sample No.	Cmax (ng/ml)	Tmax (hr)	T1/2 (hr)	AUCinf (ng·hr/ml)
1	169 (10)	0.6 (0.1)	2.6 (0.2)	467 (23)
Control	120 (16)	2.3 (0.4)	2.5 (0.2)	467 (37)

Figures in parentheses indicate the standard error.

As is clear from Table 5, the sample reached Tmax (time to reach the maximum concentration in the blood) in a shorter amount of time than the control sample, and Cmax (maximum blood concentration) was also higher.

Test Example 4

Tablet hardness was measured as determined by a hardness meter (Schleuniger-4M) using one tablet each of Embodiments 6, 7, 8 and 9 for Samples 1-4.

(Results)

The results are shown in Table 6.

Table 6

Sample No.	Tablet forming pressure (tons)		
	1	1.2	1.4
1	6.5	7.8	9.8
2	6.0	7.5	9.5
3	3.5	4.0	4.5
4	7.5	9.5	12.3

(Units: kg)

The tablets exhibited a suitable degree of hardness of 6.0 or higher.

12/12